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Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Ivemend

fosaprepitant

Procedure no.: EMA/H/C/743/P46 025
EMA/H/C/743/P46 026

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On May 21, 2017, the MAH submitted two completed paediatric studies for Ivemend (fosaprepitant), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that P029 ("*A Phase IIb, Partially-Blinded, Randomized, Active Comparator-Controlled Study to Evaluate the Pharmacokinetics/Pharmacodynamics, Safety, and Tolerability of Fosaprepitant in Pediatric Subjects for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) Associated with Emetogenic Chemotherapy*") and ONO-7847-03 ("*Japanese Clinical Study in Pediatric Patients Multicenter, open-label, uncontrolled study for the prevention of CINV"*) are part of a clinical development program. The application consisting of the full relevant data package (i.e. containing several studies) is expected to be submitted by 3Q2017. A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the studies

Fosaprepitant was supplied as a 150 mg vial to be reconstituted and then diluted prior to administration.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted final reports for:

- Study P029 entitled "A Phase IIb, Partially-Blinded, Randomized, Active Comparator-Controlled Study to Evaluate the Pharmacokinetics/Pharmacodynamics, Safety, and Tolerability of Fosaprepitant in Paediatric Subjects for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) Associated with Emetogenic Chemotherapy";

  The study was a worldwide, multicentre, partially-blinded, randomized, parallel-group, PK/pharmacodynamic (PD), dose-ranging study, to evaluate the PK, PD, and safety and tolerability of aprepitant, after administration of a single dose of fosaprepitant concomitantly with IV ondansetron, with or without dexamethasone. Protocol 029 evaluated multiple IV fosaprepitant doses in paediatric subjects from birth to 17 years of age, and was amended to include an open-label evaluation of the PK and safety/tolerability of a 5 mg/kg fosaprepitant dose in children birth to <12 years of age. An additional evaluation of the PK of dexamethasone in infants birth to <1 year of age was also included in the amendment.

- *Study ONO-7847-03 entitled "Japanese Clinical Study in Paediatric Patients Multicenter, open-label, uncontrolled study for the prevention of CINV";*

  The study is a small (n=27) prospective, uncontrolled open-label study of fosaprepitant in children 6 months to 18 years of age in a Japanese population. In this study, 3 mg/kg (to a maximum of 150 mg) fosaprepitant IV was administered to patients 6 months to <12 years of

age and 150 mg IV to subjects 12 to 18 years of age in combination with a 5-HT3 antagonist on Day 1 and corticosteroids on Days 1 to 3.

2.3.2. Clinical studies

In accordance with Article 46, the MAH submitted two study reports which are further reviewed below.

Study P029 "A Phase IIb, Partially-Blinded, Randomized, Active Comparator-Controlled Study to Evaluate the Pharmacokinetics/Pharmacodynamics, Safety, and Tolerability of Fosaprepitant in Paediatric Subjects for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) Associated with Emetogenic Chemotherapy"

Methods

Objectives

The MAH states that the primary objectives of this study were to estimate aprepitant plasma concentration profiles and PK parameters and to evaluate the safety and tolerability of fosaprepitant, administered concomitantly with a 5-HT3 antagonist, in paediatric patients from birth to 17 years old receiving emetogenic chemotherapy. The secondary objective was to estimate IV dexamethasone plasma concentration profiles and PK parameters in paediatric patients from birth to 1 year old receiving emetogenic chemotherapy, concomitant dexamethasone, and IV ondansetron, in the presence or absence of fosaprepitant.

According to MAH cover letter was P029 designed to support the United States paediatric requirements.

Study design

Protocol 029 was a Phase 2b, worldwide, multicentre, partially-blinded, randomized, parallel-group, PK/PD, dose-ranging study, to evaluate the PK, PD, and safety and tolerability of aprepitant, after administration of a single dose of fosaprepitant concomitantly with IV ondansetron, with or without dexamethasone (physician's choice). Subjects 12-17 years old in the partially-blinded portion of the trial were randomized to receive either 150 mg, 60 mg, or 20 mg of fosaprepitant or matching placebo during Cycle 1. Subjects <12 years old were randomised to 3 mg/kg, 1.2 mg/kg or 0.4 mg/kg of fosaprepitant or matching placebo. Subjects enrolled under the open-label amendment received one dose (5 mg/kg) of fosaprepitant during Cycle 1. At the discretion of the investigator, subjects were then invited to receive open-label fosaprepitant in cycles 2 to 6, which 153 subjects did.

Subjects were randomized/allocated at 49 sites. Thirty-five were allocated in Europe (including 4 sites in Russia) and 7 sites in the United States.

The PK sampling of subjects in the fosaprepitant treatment groups was randomly determined upon subject randomization. For subjects from whom PK samples were drawn, the investigator and Sponsor were unblinded to the subject's treatment with fosaprepitant; however, they remained blinded to the dose level of fosaprepitant administered. For subjects from whom no PK samples were drawn, the investigator and Sponsor remained blinded to the treatment regimen (i.e. fosaprepitant or placebo) to which the subject was randomized.

Study design and power preclude evaluation of efficacy.

Study population /Sample size

Included patients (n=240) were scheduled to receive chemotherapy high risk of emetogenicity. Subjects <2 years of age were not permitted to participate until PK and safety data from the older age cohorts (2 to 17 years of age) were analysed to confirm the planned dose adjustments. After the interim analysis the study had an open-label amendment to include a single 5 mg/kg treatment arm. Because the adolescent cohort was fully enrolled prior to the interim analysis, only subjects birth to <12 years old were included in the 5 mg/kg-arm.

Treatments

Dose selection
The approved dose recommendation of Ivemend® is a single iv dose of 150 mg over 20-30 min in adults, in conjunction with a 5-HT3 antagonist and a corticosteroid.

A popPK (population pharmacokinetic) model of aprepritant has previously been developed based on three completed studies, oral administration of aprepritant (capsule) to adolescent (P097), patients from 0.5-17 years receiving oral administration of aprepitant (suspension; P148) and paediatric patients, 0.5-17 years, receiving either oral aprepitant (suspension) or IV fosaprepitant (P134). The popPK analysis was assessed in procedure EMEA/H/C/527/X/49/G and the model was concluded to adequately describe the observed data across all age categories.

The popPK data were used for dose selection in paediatric patients to approximately match the exposure in adults following the recommended single iv dose of 150 mg fosaprepitant. A 150-mg dose was chosen as the highest dose for adolescents but with two further lower dose levels of 60 and 20 mg to be administered. For patients 4 mon to <12 years a 3 mg/kg (up to 150 mg) dose was selected as the highest and with two additional lower dose levels of 1.2 mg /kg (up to 60 mg) and 0.4 mg/kg (up to 20 mg) to be given. An interim analysis indicated lower exposure in younger children than predicted resulting in that the highest dose in 4 months to <12 years old patients was revised to 5 mg/kg.

The PK following either iv or oral administration of fosaprepitant and aprepritant, respectively, in subjects younger <4 month has not been studied. Thus, the proposed doses in <4 months old subjects was modified due to immature expression of CYP3A4, the enzyme responsible for the metabolism aprepritant. In subjects 1-4 months of age, the dose was to be reduced by 50% to 2.5 mg/kg and in subjects birth to 1mon of age reduced by 75% to 1.25 mg/kg.

Table 1 summarizes dose levels evaluated.

Table 1 Fosaprepitant doses, administered as iv infusion over 30 and 60 min in teenagers and children <12 years, respectively

Fosaprepitant Dose Arm	Age-Specific Dose Adjustments				
			0 to <2 years of age		
	12 to 17 years	2 to <12 years	4 months to <2 years	1 to <4 months	0 to <1 month
Dose 1	150 mg	3 mg/kg (up to 150 mg)	3 mg/kg[A]	1.5 mg/kg[A]	0.75 mg/kg[A]
Dose 2	60 mg	1.2 mg/kg (up to 60 mg)	1.2 mg/kg[A]	0.6 mg/kg[A]	0.3 mg/kg[A]
Dose 3	20 mg	0.4 mg/kg (up to 20 mg)	0.4 mg/kg[A]	0.2 mg/kg[A]	0.1 mg/kg[A]
Dose 4[B]	Not applicable[C]	5 mg/kg	5 mg/kg	2.5 mg/kg	1.25 mg/kg

[A] The 0 to <2 year old cohort was not open for enrollment in Amendment 01.
[B] Not to exceed 150 mg
[C] The 12 to <17 year old cohort was not open for enrollment in Amendment 04.

According to the study report, the infusion time for subjects 12 to 17 years old was 30 minutes in duration, while that for subjects <12 years old was 60 minutes. The use of a longer infusion time for the younger children was to mitigate the predicted higher maximum concentration (Cmax) to area under the concentration-time curve (AUC) ratio in young children compared to adults. By extending the infusion duration to 60 minutes for these younger children, the predicted peak aprepitant concentrations would be reduced to levels similar to that of adults.

Subjects >6 months old on Cycle 1 Day 1 were administered three 0.15 mg/kg doses of IV ondansetron, up to the maximum daily dose specified in the local product label for paediatric usage or local standard of care. For subjects <6 months old, IV ondansetron was administered per local standard of care. Dexamethasone IV was permitted at the discretion of the investigator for subjects in all treatment groups. The dose of dexamethasone was reduced to 50% of the usual prescribed dose for the 48 hours following administration of 150 mg, 3 mg/kg, or 5 mg/kg fosaprepitant dose.

Outcomes/endpoints

According to the MAH the "All Subjects as Treated (ASaT)" population was used for the analysis of safety data, and included all randomized/allocated subjects who received at least 1 dose of study medication.

Any vomiting or use of rescue therapy within a phase of treatment (acute or delayed) defined a subject as having an unfavourable response for that phase and for the overall analysis (regardless of missing data at other time points) for all efficacy subject populations.

Safety and tolerability were assessed by clinical review of all relevant parameters, including AEs, laboratory tests, vital signs, and ECG measurements.

Results

Baseline data

In total 240 patients were included but 6 patients was never administered the study medication (1 each in 3 mg/kg, 1.2 mg/kg and 0.4 mg/kg-group, and 3 in the control group) which leaves 234 patients in the All Subject as Treated (ASaT)-group.

Table 2 Subject Characteristics in Cycle 1, All Subjects as Treated

	Fosaprepitant 3mg/kg Regimen		Fosaprepitant 1.2mg/kg Regimen		Fosaprepitant 0.4mg/kg Regimen		Control Regimen		Fosaprepitant 5mg/kg Regimen		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	42		43		40		35		74		234	
Gender												
Male	24	(51.7)	20	(46.5)	21	(52.5)	18	(51.4)	42	(56.8)	125	(53.4)
Female	18	(42.9)	23	(53.5)	19	(47.5)	17	(48.6)	32	(43.2)	109	(46.6)
Age (Months)												
birth to <2 years	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	23	(31.1)	23	(9.8)
2 to <6 years	8	(19)	10	(23.3)	10	(25)	9	(25.7)	26	(35.1)	63	(26.9)
6 to <12 years	17	(40.5)	16	(37.2)	13	(32.5)	9	(25.7)	25	(33.8)	80	(34.2)
12 to 17 years	17	(40.5)	17	(39.5)	17	(42.5)	17	(48.6)	0	(0)	68	(29.1)
Mean	124.5		121.6		120.7		124.3		60.2		103.0	
SD	51.8		51.3		54.0		55.7		42.3		57.4	
Median	123.5		127.0		129.0		140.0		54.0		102.0	
Range	29-210		38-202		27-209		28-206		4-142		4-210	

The low percentage of subjects birth to <2years old was, according to the MAH, due in part to the fact that this cohort was never opened for enrolment in the partially-blinded amendment. Enrolment for subjects 12 to 17 years old was completed during the partially-blinded amendment; therefore they were not included in the fosaprepitant 5 mg/kg treatment group. No subjects less than 4 months of age were enrolled in the study

Because of the prophylactic benefit of intravenous dexamethasone in the prevention of CINV, subjects were also stratified by planned use of dexamethasone. Of those subjects who did receive prophylactic dexamethasone in Cycle 1, use was similar between the 5 treatment groups.

Pharmacokinetics

Systemic exposure of aprepritant, calculated by noncompartmental analysis, following single iv infusion of fosaprepitant concomitantly with iv ondansetron, with or without dexamethasone in paediatric patients are summarized in Table 3. Exposure in adults after a 20-min iv infusion of fosaprepitant 150 mg (study protocol 165) has been added by the MAH for comparison.

Comparable total systemic exposures of aprepitant are seen in teenagers and adults after an iv infusion of 150 mg fosparepitant. A slightly lower Cmax was seen in the teenagers compared to in the adults but the infusion time was 30 and 20 min, respectively.

The 3 mg/kg up to 150 mg dose resulted in lower exposure of aprepitant in children <12 years, the younger the lower, than in adults.

After the 5 mg/kg up to 150 mg, the children birth to <2 years showed comparable total exposure to adults after 150 mg. In the age group 2 to <6 years, about a 25% higher exposure was seen compared to in adults while the 3 mg/kg (up to 150 mg) dose resulted in about 65% lower exposure than in adults.

Table 3 Summary of exposure of aprepritant in paediatric patients following iv doses of fosaprepitant concomitantly with iv ondansetron, with or without dexamethasone. The infusion time was 30 and 60 min in teenagers and children <12 years, respectively. Historical data on exposure in adults following a 20-min iv infusion of fosaprepitant 150 mg are presented (P165)

PK Parameter	Age Group	N	GM (95% CI)	GMR vs. Adult (90% CI)
5.0 mg/kg (up to 150 mg)				
AUC0-∞ (ng•hr/mL)	Birth to <2 years	16	34200 (27100, 43100)	0.97 (0.79, 1.20)
	2 to <6 years	20	43300 (36300, 51600)	1.23 (1.04, 1.46)
	6 to <12 years	13	54100 (47200, 61900)	1.54 (1.34, 1.77)
	Adult	41	35100 (31500, 39200)	
Cmax (ng/mL)	Birth to <2 years	22	3280 (2730, 3930)	0.82 (0.69, 0.97)
	2 to <6 years	25	3800 (3110, 4630)	0.95 (0.79, 1.13)
	6 to <12 years	24	4090 (3470, 4800)	1.02 (0.88, 1.19)
	Adult	41	4010 (3680, 4370)	
150 mg or 3.0 mg/kg (up to 150 mg)				
AUC0-∞ (ng•hr/mL)	2 to <6 years	5	13100 (6550, 26300)	0.37 (0.22, 0.64)
	6 to <12 years	8	29200 (17300, 49200)	0.83 (0.54, 1.27)
	12 to 17 years	3	33300 (19600, 56600)	0.95 (0.69, 1.31)
	Adult	41	35100 (31500, 39200)	
Cmax (ng/mL)	2 to <6 years	6	1960 (1010, 3790)	0.49 (0.29, 0.82)
	6 to <12 years	14	2930 (2040, 4210)	0.73 (0.54, 0.99)
	12 to 17 years	12	3360 (2740, 4110)	0.84 (0.70, 1.00)
	Adult	41	4010 (3680, 4370)	
60 mg or 1.2 mg/kg (up to 60 mg)				
AUC0-∞ (ng•hr/mL)	2 to <6 years	5	13400 (5590, 32200)	0.38 (0.20, 0.75)
	6 to <12 years	9	9370 (6030, 14600)	0.27 (0.19, 0.38)
	12 to 17 years	8	11600 (8460, 15800)	0.33 (0.25, 0.43)
	Adult	41	35100 (31500, 39200)	
Cmax (ng/mL)	2 to <6 years	8	1600 (906, 2840)	0.40 (0.25, 0.63)
	6 to <12 years	13	1140 (786, 1650)	0.28 (0.21, 0.39)
	12 to 17 years	12	1110 (869, 1420)	0.28 (0.22, 0.34)
	Adult	41	4010 (3680, 4370)	
20 mg or 0.4 mg/kg (up to 20 mg)				
AUC0-∞ (ng•hr/mL)	2 to <6 years	4	1890 (857, 4170)	0.05 (0.03, 0.10)
	6 to <12 years	8	2650 (1840, 3820)	0.08 (0.06, 0.10)
	12 to 17 years	9	3310 (2560, 4280)	0.09 (0.08, 0.12)
	Adult	41	35100 (31500, 39200)	
Cmax (ng/mL)	2 to <6 years	6	309 (219, 436)	0.08 (0.06, 0.10)
	6 to <12 years	12	407 (272, 610)	0.10 (0.07, 0.14)
	12 to 17 years	13	467 (310, 703)	0.12 (0.08, 0.16)
	Adult	41	4010 (3680, 4370)	

Efficacy results

The study had not the power, nor the design, to allow a reliable evaluation of efficacy.

Cycle 1 data was used for the evaluation of efficacy as an exploratory endpoint. No efficacy evaluation was performed for Cycles 2 through 6.

Complete Response (CR), defined as no vomiting, no retching, and no use of rescue medication, was evaluated for the acute (0 to 24 hours), delayed (25 to 120 hours) and overall (0 to 120 hours) phases following initiation of emetogenic chemotherapy in Cycle 1.

Table 4 Number (%) of Subjects with Complete Response in the Acute Phase in Cycle 1 by Treatment Regimen, Intent to Treat Population

Treatment	n/m (%)	Difference (%)†	95% CI for Difference
Partially Blinded:			
Fosaprepitant 3mg/kg Regimen	27/42 (64.3)	24.3	(-1.6,50.0)
Fosaprepitant 1.2mg/kg Regimen	24/43 (55.8)	15.8	(-7.6,41.9)
Fosaprepitant 0.4mg/kg Regimen	30/40 (75.0)	35.0	(21.0,64.1)
Control Regimen	14/35 (40.0)		
Open-Label:			
Fosaprepitant 5mg/kg Regimen	60/74 (81.1)		

† Fosaprepitant regimen – Control regimen.

‡ Confidence interval (CI) for the difference was calculated using the method proposed by Miettinen and Nurminen, accounting for dose and dexamethasone use (yes/no).

n/m = Number of subjects with desired response/number of subjects included in time point

Acute Phase: 0 to 24 hours following initiation of chemotherapy.

Partially Blinded:

For Fosaprepitant 3mg/kg Regimen, subjects 12-17 years of age received a fixed 150 mg fosaprepitant dose.

For Fosaprepitant 1.2mg/kg Regimen, subjects 12-17 years of age received a fixed 60 mg fosaprepitant dose.

For Fosaprepitant 0.4mg/kg Regimen, subjects 12-17 years of age received a fixed 20 mg fosaprepitant dose.

Source: [P029MK0517: analysis-adeff]

Table 5 Number (%) of Subjects with Complete Response in the Overall Phase in Cycle 1 by Treatment Regimen, Intent to Treat Population

Treatment	n/m (%)	Difference (%)†	95% CI for Difference (%)‡
Partially Blinded:			
Fosaprepitant 3mg/kg Regimen	13/42 (31.0)	11.0	(-18.2,29.3)
Fosaprepitant 1.2mg/kg Regimen	8/43 (18.6)	-1.4	(-23.2,21.9)
Fosaprepitant 0.4mg/kg Regimen	14/40 (35.0)	15.0	(-10.7,38.1)
Control Regimen	7/35 (20.0)		
Open-Label:			
Fosaprepitant 5mg/kg Regimen	33/74 (44.6)		

† Fosaprepitant regimen – Control regimen.

‡ Confidence interval (CI) for the difference was calculated using the method proposed by Miettinen and Nurminen, accounting for dose and dexamethasone use (yes/no).

n/m = Number of subjects with desired response/number of subjects included in time point

Overall Phase: 0 to 120 hours following initiation of chemotherapy.

Partially Blinded:

For Fosaprepitant 3mg/kg Regimen, subjects 12-17 years of age received a fixed 150 mg fosaprepitant dose.

For Fosaprepitant 1.2mg/kg Regimen, subjects 12-17 years of age received a fixed 60 mg fosaprepitant dose.

For Fosaprepitant 0.4mg/kg Regimen, subjects 12-17 years of age received a fixed 20 mg fosaprepitant dose.

Source: [P029MK0517: analysis-adeff]

Even though no clear connection is seen between fosaprepitant-dose and response rate the proportions of subjects with CR in the acute phase were higher in the fosaprepitant group compared with the control regimen. In the open-label amendment, the proportion of subjects with CR in the acute phase was 81.1%.

Safety results

The ASaT population was used for the analysis of safety data. All AEs were reported by the investigators from the time of subject randomization through 14 days following cessation of treatment. Events related to the efficacy endpoint of Complete Response (vomiting, dry heaves) were not defined as AEs during the initial period of 120 hours following chemotherapy unless they met the definition of a serious adverse event (SAE). Beyond this period, vomiting and dry heaves were considered AEs.

Adverse events were reported by 133 (83.1%) of the 160 subjects in the safety analysis in Cycle 1 for the partially-blinded amendment. A higher number of subjects in the fosaprepitant treatment groups had 1 or more reported AEs, while a higher number of subjects in the control regimen reported SAEs. The assessment of differences between fosaprepitant versus control is in line with conclusions from the MAH, that estimated differences between fosaprepitant versus control were minimal. Because subjects were enrolled in a single-treatment arm in the open-label amendment, analysis of AEs for fosaprepitant vs. control was not applicable.

When all patients were included in the safety analysis, adverse events were reported by 198 (84.6%) of the 234 subjects in Cycle 1. Although there was some variability between treatment regimens in the proportion of subjects with AEs, there were no patterns noted. No serious drug-related AEs, deaths, or discontinuations due to AEs were reported for any subjects during Cycle 1 of the partially-blinded amendment. In the open-label amendment, 1 subject receiving fosaprepitant 5 mg/kg in the 2 to <6 years old category was reported to have a drug-related SAE and discontinued due to the AE.

Table 6 Adverse Event Summary in Cycle 1, All Subjects as Treated

	Fosaprepitant 3mg/kg Regimen		Fosaprepitant 1.2mg/kg Regimen		Fosaprepitant 0.4mg/kg Regimen		Control Regimen		Fosaprepitant 5mg/kg Regimen		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	42		43		40		35		74		234	
with one or more adverse events	35	(83.3)	39	(90.7)	32	(80.0)	27	(77.1)	65	(87.8)	198	(84.6)
with no adverse event	7	(16.7)	4	(9.3)	8	(20.0)	8	(22.9)	9	(12.2)	36	(15.4)
with drug-related[†] adverse events	2	(4.8)	3	(7.0)	4	(10.0)	3	(8.6)	4	(5.4)	16	(6.8)
with serious adverse events	12	(28.6)	14	(32.6)	11	(27.5)	12	(34.3)	24	(32.4)	73	(31.2)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.4)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued[‡] due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.4)
discontinued due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.4)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.4)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.4)

[†] Determined by the investigator to be related to the drug.

[‡] Study medication withdrawn.

For Fosaprepitant 3mg/kg Regimen, subjects 12-17 years of age received a fixed 150 mg fosaprepitant dose.

For Fosaprepitant 1.2mg/kg Regimen, subjects 12-17 years of age received a fixed 60 mg fosaprepitant dose.

For Fosaprepitant 0.4mg/kg Regimen, subjects 12-17 years of age received a fixed 20 mg fosaprepitant dose.

Source: [P029MK0517: analysis-adsl] [P029MK0517: tabulations-aeplus]

A higher proportion of patients in the Ivemend treatment groups experienced an AE compared to the lower proportion of AEs in the placebo control group, but the latter included a higher proportion of drug

related adverse events compared to most of the Ivemend groups. No pattern is recognised between Ivemend use/dose and proportion of AEs.

Table 7 Subjects With Drug-Related Adverse Events, (Incidence > 0% in One or More Treatment Groups) in Cycle 1, All Subjects as Treated

	Fosaprepitant 3mg/kg Regimen		Fosaprepitant 1.2mg/kg Regimen		Fosaprepitant 0.4mg/kg Regimen		Control Regimen		Fosaprepitant 5mg/kg Regimen		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	42		43		40		35		74		234	
with one or more drug- related adverse events	2	(4.8)	3	(7.0)	4	(10.0)	3	(8.6)	4	(5.4)	16	(6.8)
with no drug-related adverse events	40	(95.2)	40	(93.0)	36	(90.0)	32	(91.4)	70	(94.6)	218	(93.2)
Cardiac disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.4)**	**1**	**(0.4)**
Bradycardia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.4)
Gastrointestinal disorders	**1**	**(2.4)**	**1**	**(2.3)**	**0**	**(0.0)**	**1**	**(2.9)**	**0**	**(0.0)**	**3**	**(1.3)**
Abdominal pain	0	(0.0)	1	(2.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Dyspepsia	1	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Vomiting	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)	1	(0.4)
General disorders and administration site conditions	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(2.5)**	**1**	**(2.9)**	**0**	**(0.0)**	**2**	**(0.9)**
Fatigue	0	(0.0)	0	(0.0)	1	(2.5)	1	(2.9)	0	(0.0)	2	(0.9)
Immune system disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.4)**	**1**	**(0.4)**
Anaphylactic reaction	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.4)
Investigations	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(5.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.9)**
Alanine aminotransferase increased	0	(0.0)	0	(0.0)	2	(5.0)	0	(0.0)	0	(0.0)	2	(0.9)
Investigations	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(5.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.9)**
Aspartate aminotransferase increased	0	(0.0)	0	(0.0)	1	(2.5)	0	(0.0)	0	(0.0)	1	(0.4)
Nervous system disorders	**1**	**(2.4)**	**1**	**(2.3)**	**1**	**(2.5)**	**0**	**(0.0)**	**1**	**(1.4)**	**4**	**(1.7)**
Dizziness	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.4)
Extrapyramidal disorder	1	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Headache	0	(0.0)	1	(2.3)	1	(2.5)	0	(0.0)	1	(1.4)	3	(1.3)
Respiratory, thoracic and mediastinal disorders	**1**	**(2.4)**	**1**	**(2.3)**	**1**	**(2.5)**	**1**	**(2.9)**	**1**	**(1.4)**	**5**	**(2.1)**
Hiccups	1	(2.4)	1	(2.3)	1	(2.5)	1	(2.9)	1	(1.4)	5	(2.1)
Skin and subcutaneous tissue disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(2.9)**	**1**	**(1.4)**	**2**	**(0.9)**
Pruritus generalised	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)	1	(0.4)

	Fosaprepitant 3mg/kg Regimen		Fosaprepitant 1.2mg/kg Regimen		Fosaprepitant 0.4mg/kg Regimen		Control Regimen		Fosaprepitant 5mg/kg Regimen		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Rash	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.4)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
For Fosaprepitant 3mg/kg Regimen, subjects 12-17 years of age received a fixed 150 mg fosaprepitant dose.
For Fosaprepitant 1.2mg/kg Regimen, subjects 12-17 years of age received a fixed 60 mg fosaprepitant dose.
For Fosaprepitant 0.4mg/kg Regimen, subjects 12-17 years of age received a fixed 20 mg fosaprepitant dose.

Source: [P029MK0517: analysis-adsl] [P029MK0517: tabulations-aeplus]

Six subjects (3.9%) had drug-related AEs in Cycles 2 to 6. The incidence of drug-related AEs for Cycles 2 to 6 was similar to the results for Cycle 1. The only AE that occurred in more than 1 subject was hiccups. One subject had a drug-related AE of seizure that was considered to be a SAE.

Serious adverse events were reported in 73 subjects (31.2%) for Cycle 1. The most commonly reported SAEs occurred in the blood and lymphatic system disorders SOC, with febrile neutropenia occurring most frequently. No dose-related pattern was noted for febrile neutropenia incidence. The SAE profile was typical of a patient population with cancer receiving chemotherapy. One subject in the fosaprepitant 5 mg/kg treatment group in Cycle 1 had a SAE of anaphylactic reaction that was determined by the investigator to be drug-related.

No subject deaths were reported in Cycle 1. Two subject deaths were reported in Cycles 2 to 6. One subject in the fosaprepitant 3 mg/kg regimen died due to a SAE of neutropenia during the Cycle 4 follow-up period. One subject in the fosaprepitant 3 mg/kg regimen died due to a SAE of metastases to lung after receiving 4 cycles of study medication.

Study ONO-7847-03 "Japanese Clinical Study in Pediatric Patients Multicenter, open-label, uncontrolled study for the prevention of CINV";

Methods

Objectives

The study objective was to confirm the safety, efficacy, and PK-data of ONO-7847 in the prevention of CINV.

According to MAH cover letter, protocol ONO-7847-03 was conducted to support approval of fosaprepitant in Japan for the prevention of CINV in paediatric patients.

Study design

The ONO-7847-03 study was a multicentre, uncontrolled, open-label, single-arm trial.

Study population /Sample size

The study included 27 paediatric Japanese patients 6 months to 18 years old (12- to 18-years old: n=12; 6- to 11-years old: n=5; 2- to 5-years old: n=5; 6-months to 1-year old: n=5) with malignant tumours scheduled to receive chemotherapy.

Treatments

A single IV dose of fosaprepitant meglumine was administered at a dose of 150 mg to 12- to 18-year-old subjects and 3 mg/kg (up to a maximum of 150 mg) to 6-month to 11-year-old subjects. Granisetron and dexamethasone were administered as standard therapy in all subjects.

Table 8 Treatment groups ONO-7847-03

	12 years to 18 years	6 months to 11 years
ONO-7847	Day 1: 150 mg	Day 1: 3.0 mg/kg*1
Dexamethasone phosphate	Days 1-2: 4 mg Day 3: 8 mg	Days 1-2: 0.1 mg/kg*2 Day 3: 0.2 mg/kg*3
Granisetron	Day 1: 40 μg/kg (Days 2 to 5: 40 μg/kg)*4	

*1: Up to a maximum of 150 mg
*2: Up to a maximum of 4 mg
*3: Up to a maximum of 8 mg
*4: Preventive treatment with granisetron (40 μg/kg) was permitted on the day of treatment with any of cisplatin, cyclophosphamide, or carboplatin, or moderately or highly emetogenic chemotherapy.

Outcomes/endpoints

Efficacy was evaluated during the acute phase (0-24 hours), the delayed phase (24-120 hours) and overall (0-120 hours). Vomiting, nausea and use of rescue therapy was measured.

Safety evaluation included AE and SAE overall and due to study medication, clinical laboratory tests, vital signs and ECG. Further plasma concentrations of ONO-7847 and aprepitant were measured and pharmacokinetic parameters of aprepitant in plasma investigated.

Results

Efficacy results

It should be noted that this study was not powered to measure efficacy, and was a single-arm, open-label study with no control group for comparison.

Efficacy was evaluated as a primary endpoint. For the primary analysis of efficacy the following population was used; all subjects who met key enrolment criteria, received at least 1 dose of both granisetron and dexamethasone phosphate, received any of cisplatin, cyclophosphamide, or carboplatin, received at least 1 dose of investigational product, and had at least 1 post-treatment efficacy observation.

Safety results

The incidence of AEs was 100.0%, and the incidence of drug-related AEs was 14.8%. The most common AE was lymphocyte count decreased (96.3%). No deaths were reported in this study. Serious adverse events occurred in 2 subjects (7.4%), but no drug-related SAEs were reported. No abnormalities in vital signs, 12-lead ECGs, or body weight resulted in any safety issues.

2.3.3. Discussion on clinical aspects

Protocol 029 and ONO-7847-03 were designed to support the United States paediatric requirements and the approval of fosaprepitant in Japan. Both studies were conducted with the intention to evaluate PK- and safety data whereas study design and power precluded statistical evaluation of efficacy.

There was an amendment filed to increase fosaprepitant dose to 5 mg/kg for certain age groups in study 029. This entails change of study design and complicates comparison between Ivemend treatment arms and the control arm. The rationale for an optional enrolment for cycle 2 to 6 is not fully comprehensible, even though the design does not severely hamper the primary objectives.

The dose selection was based on popPK analysis aiming for exposure in children to be comparable to the exposure in adults following the recommended single iv dose of 150 mg fosaprepitant. A 150-mg dose was chosen as the highest dose for adolescents but with two further lower dose levels of 60 and 20 mg to be administered. For patients 4 months to <12 years a 3 mg/kg (up to 150 mg) dose was selected as the highest and two additional dose levels of 1.2 mg /kg (up to 60 mg) and 0.4 mg/kg (up to 20 mg) to be given. An interim analysis indicated lower exposure in younger children than predicted resulting in that the highest dose in 4 months to <12 years old patients was revised to 5 mg/kg.

The approved indication of Ivemend for adults permits administration in a peripheral vein. However, in study P029 Ivemend was administered via central venous catheters for all subjects. This could contribute to that some side effects, like rash at the infusion site, do not occur.

The other antiemetic regimens consisting of 5HT-3 antagonist and possible glucocorticoids, is considered adequate. Stratification by dexamethasone administration is endorsed.

The MAH states that overall, the data for P029 supports the conclusion that the single-day IV fosaprepitant regimen was generally well tolerated in paediatric subjects receiving emetogenic chemotherapy. The overall pattern of clinical and laboratory AEs in the Ivemend-arm was similar to that observed for the control regimen, as well as to that typically observed in paediatric subjects receiving chemotherapy, and to that observed in the aprepitant clinical development program.

No notable differences in the safety or tolerability profiles were observed among age subgroups. Safety signals reported are consistent with the already known safety profile of Ivemend. However the pattern of specific AEs cannot be properly assessed due to few AEs in each SOC category.

Results from study ONO-7847-03 was in line with those in Protocol 029.

3. Rapporteur's overall conclusion and recommendation

In accordance with Article 46, the MAH hereby submits two studies (study 029 and ONO-7847-03) in which the PK, safety and tolerability of Ivemend was evaluated in children 4 months to <18 years of age. Neither study was designed to evaluate efficacy.

The overall assessment of these two studies are that the safety profile of Ivemend for children below 18 years of age, for the doses administered in the studies, is in line with previously known safety profiles for adults.

☒ Fulfilled:

No regulatory action required.

4. Additional clarification requested

None